REMARKS

The Substitute Specification is amended with a brief description of two existing drawings. Support for the amendment is found in FIGS. 4A and 4B and in the specification as originally filed at page 21, lines 13-14.

Claims 40-42 and 44-61 were pending in this application. New claims 62 and 63 are added. Claims 46, 49, 53, 54, 57, 59, and 60 are amended without any intent of disclaiming equivalents thereof. And claims 40-42, 44, 45, 47, 48, and 50-52 are canceled without prejudice. Accordingly, upon entry of this paper, claims 46, 49, and 53-63 are pending and presented for reconsideration.

Support for the new claims 62 and 63 can be found in the Substitute Specification at least at paragraphs 58 and 59 on pages 11 and 12. Reference to the Specification hereafter, unless specified, refers to the Substitute Specification filed on March 6, 2002. Claims 46, 49, and 53 are amended with formal changes. Support for amendment to claim 54 can be found in the Specification at least at paragraph 81 on page 18. Claims 57, 59, and 60 are amended to conform with their base claim, amended claim 54. Applicant respectfully submits that the amendments to the Specification and the claims do not introduce new matter.

Priority

A Supplemental Application Data Sheet is submitted herewith as suggested by the Office action. Applicant respectfully submits that any implied objections regarding the formality involved in claiming priority have been overcome and should be withdrawn.

Specification

The specification is objected to because the description of the drawings does not contain a reference to both Figures 4A and 4B. Applicant has amended the specification through the instant Amendment, and respectfully submits that the objection over the specification has been overcome and should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 40-42, 44-46, and 53 are rejected under 35 U.S.C. § 112, second paragraph, for being indefinite. Specifically, for example, the Office action rejects claim 46 stating that the relationship between the preamble and the recited step is not set forth. Through this paper, Applicant has amended claim 46 by expressly reciting a step where an increased risk of developing thrombosis, as referred to in the preamble, is determined based on the comparison step. Therefore, Applicant respectfully submits that the rejection over claim 46 has been overcome through the amendment, and should be withdrawn.

Claim 53 is also rejected for not specifying the antecedent basis for the phrase "the Factor V gene" as the base claim recites two different "Factor V genes." Applicant has amended claim 53 to specifically recite "the individual's Factor V gene." Accordingly, Applicant respectfully submits that the rejection over claim 53 has been overcome through the amendment, and should be withdrawn.

Applicant has canceled, without prejudice, all the other claims rejected under 35 U.S.C. § 112, second paragraph, namely, claims 40-42, 44, and 45. Therefore, Applicant respectfully submits that all the rejections under 35 U.S.C. § 112, second paragraph, are either overcome or moot, and requests the withdrawal of rejections of claims 40-42, 44-46, and 53.

Rejections under 35 U.S.C. § 112, first paragraph

1. Claims 40-42 and 44-61 stand rejected under 35 U.S.C. § 112, first paragraph. The Office action states that the subject matter of these claims is not described in the specification in an enabling manner. Applicant addresses these rejections below to the extent they are maintained over any of the pending claims as amended. There are two independent claims pending after this Amendment, namely, claims 46 and 54.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without

undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP, 2164.01.

The Office action recognizes that the Applicant teaches that a neutral polymorphism in the Factor V gene has shown strong linkage with inherited APC resistance, and that there is a large body of knowledge in the art related to polymorphisms and their association with diseases. However, The Office action suggests that without disclosing the precise location of the nucleotide mutation in the Factor V gene, the present claims are not enabled in view of the level of unpredictability in the art and the quantity of needed experimentation. Applicant respectfully traverses.

First, the breadth of the claims, as amended, is commensurate with the teaching. Amended claim 46 is directed to a method determining whether there is an increased *risk* of developing thrombosis. Amended claim 54 is directed to a method determining the occurrence of a Factor V gene mutation associated with Activated Protein C (APC)-resistance. In the study described by Keating in 1992[1], based on a "complete linkage" between H-*ras*-1 and long QT (LQT) syndrome, a cardiac disease, is sufficient for the author to conclude that "the H-*ras*-1 marker can be used ... for presymptomatic diagnosis of LQT" even when "no mutations have been identified in the coding sequence of the H-*ras*-1 gene in LQT patients." Keating, at 1981-82. Similarly in the present application, a "strong linkage" between a polymorphism in the Factor V gene and the phenotype of APC-resistance has been found. Specification, at 18. "Once genetic markers have been identified that are linked to the disease gene it is possible to predict the *risk* of an asymptomatic individual being a disease gene carrier." Zbar[2], at 233 (emphasis added). The present specification describes that a polymorphic marker in the Factor V gene is linked to the disease of APC-resistance, therefore, one reasonably skilled in the art could

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[1] Keating, M., "Linkage Analysis and Long QT Syndrome: Using Genetics to Study Cardiovascular Disease," *Circulation*, 85:1973-1986, (1992). A copy of this article was supplied with the Preliminary Amendment and Supplemental Response filed April 9, 2004.

[2] Zbar, B., "The Biology and Genetics of Hereditary Cancers," *Seminars in Oncology Nursing*, 8(4):229-234, (1992). A copy of this article was supplied with the Preliminary Amendment and Supplemental Response filed April 9, 2004.

use that information, to determine, based on finding "the abnormal presence or absence of one or more nucleic acid fragment(s) and /or sequence(s) for ... a Factor V molecule either carrying APC-cofactor 2 activity or being deficient in this activity," that there is an increased *risk* of developing thrombosis (claim 46), or that it is associated with APC-resistance (claim 54). Specification, at 18.

Moreover, the invention, based on the strong polymorphic linkage, further provides extensive and conclusive evidence that indeed it is the Factor V gene that is the disease-causing gene implicated by the observed polymorphism. *See* Specification, at 3-7. Before the discovery disclosed in the present invention, Factor V was only known for its procoagulant activity and "a mutation giving an APC-resistant Factor Va molecule" was ruled out in the prior art as a possible explanation for APC-resistance. Specification, at 2-3, para. 12. The present invention, however, discloses the surprising discovery of a novel anticoagulant activity of Factor V, which is contrary to the procoagulant activity of Factor V previously known in the art. Paragraph 27 of the present application summarizes how the anticoagulant activity is verified as originating from Factor V. Specification, at 5-6. Such verification included extensive assays using functional analyses, protein characterization and immunoassays, for example, coelution of Factor V's procoagulant activity and APC-related anticoagulant activity. These experimental data, coupled with the knowledge of the strong linkage between a polymorphism in the Factor V gene and the disease phenotype, allowed the Applicant to conclude that the Factor V gene is the disease-causing gene for APC resistance, and to supply one reasonably skilled in the art the information needed to make and use genetic-based assays claimed in amended claims 46 and 54.

Second, the level of predictability in the art, especially after the specific disease-causing gene has been identified, adequately facilitates one skilled in the art to use the invention. Once the disease-causing gene, the Factor V gene in this case, is identified, the remaining task of pinpointing the mutation in the Factor V gene becomes routine and "may involve many different techniques, often including PCR-SSCP or PCR-DGGE and direct sequencing." Keating, at 1985. "The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be

explicitly stated in the specification." *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004); MPEP, 2164.03. Because knowledge in the art as to how to characterize a genetic mutation once the disease-causing gene has been identified is abundant, the requisite teaching in that respect by Applicant is minimal.

It is well known in the art, for example, that the exact mutation can be located by comparing the nucleotide sequences of the disease-causing gene, Factor V in this case, between an affected individual, a patient with APC-resistance in this case, and that of a normal individual. *See* Keating, at 1981 ("Further evidence that a candidate gene like H-*ras*-1 is the disease gene can be obtained by identifying mutations in sequences derived from affected individuals."). Accordingly, the present teaching of using "nucleic hybridization assays, and DNA and RNA sequencing methods," for example, Specification, at 12, para. 59, suffices to guide the skilled artisan to practice the invention.

The Office action cited two publications, namely, "A Closer Look at SNPs Suggests Difficulties" by Pennisi (1998) *Science*, 281, 1787-89, and WO 99/52942 by Blumenfeld, *et al.*, to show the level of unpredictability in the art. First, Applicant respectfully submits that both Pennisi and Blumenfeld postdate the international filing date (January, 28, 1994) and the priority dates (July 20, 1993 and January 29, 1993) of the present application. Specifically, Pennisi was published in September 1998, and, Blumenfeld was published in October 1999. Because Pennisi and Blumenfeld were published more than five and six years, respectively, *after* the priority date of the present application, Applicant respectfully submits that neither reference provide evidence of knowledge in the art at the time of filing. *See* MPEP, 2164.05(a) ("In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling."). Therefore, Applicant respectfully submits that neither Pennisi nor Blumenfeld should be used in the analysis on whether the disclosure, *when filed*, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the art to make and use the claimed invention.

Moreover, Applicant respectfully submits that even if one were to consider Pennisi and Blumenfeld for purpose of the analysis here, neither reference serves to refute enablement by the present invention. Instead, both references support finding enablement in the present invention. Pennisi and Blumenfeld both relate to studies of associations between polymorphisms and particular diseases, and refer to potential complications in such studies. In particular, Pennisi, for example, highlights the need to look to other techniques in combination with pure polymorphism mapping. *See* Pennisi, at 1788 (quoting researchers stating that other information and technology besides single-nucleotide polymorphism (SNP) data *alone* or "just SNPs on their own" are needed for identifying a disease gene in some cases) (emphasis added). This is accomplished in the present invention as the specification not only teaches that the association between a polymorphism in the Factor V gene and the thrombosis disease has been established, it also utilizes extensive assays outside polymorphism mapping to verify that Factor V gene is the disease-causing gene. Most of the SNP studies cited in Pennisi do not include protein-based assays, for example, while the present invention include an array of assays that further characterized the proteolysis of activated Factor V by APC. *See* Specification, at 4.

At least for the above reasons, Applicant respectfully submits that all pending claims, as amended, are fully enabled by the present specification, and requests that all rejections based on the statutory "enablement" requirement over any pending claims as amended be reconsidered and withdrawn.

2. Claims 40-42 and 44-61 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly not complying with the written description requirement. The Office action states that the claimed subject matter was not described in such a way as to reasonably convey to one skilled in the relevant art that the Applicant had possession of the invention at the time of filing. Applicant addresses these rejections below to the extent they are maintained over any of the pending claims as amended.

An objective standard for determining compliance with the written description requirement is whether the description clearly allows persons of ordinary skill in the art to

recognize that he or she invented what is claimed. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 969, (Fed Cir. 2002); MPEP § 2163.02. "The written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when *coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'" *Enzo*, 323 F.3d at 963 (emphasis added) (quoting the PTO's Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement, 66 Fed. Reg. 1099, at 1106).

Applying this standard to the present application, Applicant submits that the specification of the instant application provides adequate written description of the claimed invention. The present application does not claim any particular mutation in the Factor V gene, but a method for determining whether there is an increased risk of developing thrombosis in an individual (amended claim 46), or a method for determining an occurrence of a Factor V gene mutation associated with APC-resistance in an individual (amended claim 54). Therefore, Applicant does not need to describe the structure of an unclaimed mutation in the Factor V gene.

The Office action also suggests that the specific structure of the polymorphism may be needed for purpose of meeting the written description requirement. Specifically, the Office action states that "[a] polymorphism that is associated with a particular phenotype may be linked to a particular 'disease gene' that is within the same gene as the polymorphism or that is hundreds of thousands of base pairs away from the linked polymorphism." Office action, at 11. As discussed above, the present application discloses functional assays that pinpoints a novel anticoagulant activity in the Factor V protein and the strong linkage between a known polymorphism in the Factor V gene and APC-resistance. Therefore, one skilled in the art, upon reading Applicant's application, would readily agree that Applicant has correctly concluded that the so-called "disease gene" is indeed within the same gene as the polymorphism site. Specification, at 4-5 and 18. As the present application discloses *correlation* between the anticoagulant function by the Factor V protein and polymorphism in Factor V gene, Applicant respectfully submits the specification of the instant application fully complies with the written

description requirement as is required by the current case law and the PTO's Guidelines cited above.

At least for the above reasons, Applicant respectfully requests that all rejections based on the statutory "written description" requirement over any pending claims as amended be reconsidered and withdrawn.

INFORMATION DISCLOSURE STATEMENT (IDS)

Applicant wishes to make the Patent Office aware that the parent of the instant application, U.S. Serial No. 08/500,917, is undergoing the following interference proceedings.

Patent Interference No. 105,235	Griffin *et al.* (Patent 5,705,395) v. Dahlbäck (USSN 08/500,917)
Patent Interference No. 105,268	Griffin *et al.* (Patent 5,834,223) v. Dahlbäck (USSN 08/500,917)
Patent Interference No. 105,269	Griffin *et al.* (Patent 6,083,757) v. Dahlbäck (USSN 08/500,917)

CONCLUSION

Applicant respectfully urges that all claims are in condition for allowance and requests favorable action on the present application.

Respectfully submitted,

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